

What is claimed is:

1. A method of screening for a candidate bacterial nucleic acid sequence that encodes a target polypeptide for a single-gene lysis polypeptide comprising:
 - 5 contacting bacteria with a lysis polypeptide; selecting for bacterial survivors of cell lysis caused by the lysis polypeptide that survive lysis by having a candidate bacterial nucleic acid sequence that encodes a target polypeptide making cells resistant to lysis by the lysis polypeptide; and
 - 10 mapping the candidate bacterial nucleic acid sequence, wherein the mapped sequence corresponds to the nucleic acid sequence which encodes the target polypeptide.
2. The method of claim 1, wherein contacting the bacteria with the lysis polypeptide comprises transforming bacteria with a vector comprising a nucleic acid sequence that encodes a single-gene lysis polypeptide.
- 15 3. The method of claim 2, wherein contacting comprises inducing the expression of the lysis polypeptide.
4. The method of claim 1, wherein the lysis polypeptide is mutated.
5. The method of claim 1, further comprising isolating the mapped bacterial 20 nucleic acid sequence.
6. The method of claim 5, further comprising determining the characteristics of the isolated bacterial nucleic acid sequence.
7. The method of claim 6, wherein determining the characteristics of the bacterial nucleic acid sequence comprises gel electrophoresis or nucleic 25 acid sequence analysis.

8. The method of claim 1, further comprising inserting the mapped bacterial nucleic acid sequence in an expression vector to produce a polypeptide.
9. The method of claim 8, further comprising isolating the polypeptide.
10. The method of claim 9, further comprising determining the characteristics of the polypeptide.
- 5 11. The method of claim 10, wherein determining the characteristics comprises electrophoresis, spectrophotometric analysis, amino acid analysis, structural analysis or analysis of biochemical functions.
12. The method of claim 1, wherein the bacteria comprise a vector comprising a nucleic acid sequence encoding a polypeptide involved in cell wall synthesis or synthesis of other envelope components essential for the integrity of the cell.
- 10 13. A method of screening for a bacteriophage lysis polypeptide that targets the bacterial cell wall synthesis or synthesis of other envelope components essential for the integrity of the cell comprising:
 - 15 obtaining a panel of recombinant bacterial strains, each overexpressing at least one recombinant nucleic acid sequence encoding a target polypeptide involved in cell wall synthesis or synthesis of other envelope components essential for the integrity of the cell, or a non-target polypeptide as a control;
 - 20 obtaining a candidate bacteriophage;
 - 25 contacting the panel of recombinant bacterial strains with the candidate bacteriophage;
 - selecting bacteriophage that is lysis-defective on at least one recombinant bacterial strain, wherein said bacteriophage expresses a single-gene lysis polypeptide that interacts with a target

polypeptide involved in cell wall synthesis or synthesis of other envelope components essential for the integrity of the cell; and

5 mapping a nucleic acid sequence in the bacteriophage, wherein the nucleic acid sequence encodes the single-gene lysis polypeptide.

14. The method of claim 13, further comprising isolating the nucleic acid sequence.
15. The method of claim 14, further comprising determining the characteristics of the nucleic acid sequence.
- 10 16. The method of claim 15, wherein determining the characteristics comprises gel electrophoresis or nucleic acid sequence analysis.
17. The method of claim 13, wherein obtaining a candidate bacteriophage comprises isolating the bacteriophage from sources selected from the group consisting of animal digestive tracts, fecal matter, sewage, waste water, natural salt water, fresh water and soil.
- 15 18. The method of claim 13, wherein the panel of bacterial strains comprises Gram-negative bacteria.
19. The method of claim 19, wherein the panel of bacterial strains comprises Gram-positive bacteria.
- 20 20. The method of claim 13, wherein the panel of bacterial strains comprises a combination of Gram-negative and Gram-positive bacteria.
21. The method of claim 13, wherein obtaining a panel of recombinant bacterial strains further comprises at least one mutated target polypeptide.
22. A method of screening for nucleic acid sequences which encode a single-
25 gene lysis polypeptide comprising:

obtaining a library of DNA sequences cloned into an inducible plasmid expression vector;

transforming the library into a bacterial strain

contacting the bacterial strain with polypeptides produced from the library after induction;

selecting for vector plasmids that produce lysis polypeptides, wherein the vector plasmids are released into the medium after cell lysis; and

10 determining the nucleic acid sequence encoding the lysis polypeptide from the plasmid DNA isolated from the lysed cells.

23. The method of claim 22, wherein the library of DNA sequences comprises libraries constructed from bacterial chromosomal DNA, plasmid DNA from Gram positive bacteria, plasmid DNA from Gram negative bacteria or DNA pooled from uncharacterized bacteriophages.

15 24. The method of claim 23, wherein the uncharacterized bacteriophages are isolated from the sources selected from the group consisting of animal digestive tracts, fecal matter, sewage, waste water, natural salt water, fresh water and soil.

20 25. The method of claim 23, further comprising a cDNA library, wherein the cDNA library is constructed from RNA bacteriophages.

26. A method of screening for a bacteriophage, wherein the bacteriophage has enhanced lytic activity comprising:

25 obtaining a recombinant bacterial strain, wherein the bacterial strain is transformed with a vector comprising a nucleic acid sequence encoding a recombinant target polypeptide involved in cell wall synthesis or synthesis of other envelope components essential for the integrity of the cell;

obtaining a candidate bacteriophage with a single-gene lysis polypeptide that interacts with the target polypeptide;

contacting the recombinant bacterial strain with the candidate bacteriophage;

5 selecting for survivor bacteriophages; and

mapping the bacteriophage nucleic acid sequence which encodes the single-gene lysis polypeptide.

27. The method of claim 26, wherein the target polypeptide is MurA.

28. The method of claim 26, wherein the target polypeptide is MraY.

10 29. The method of claim 26, wherein the recombinant bacterial strain further a mutated target polypeptide.

30. A polypeptide antibiotic comprising at least an amino acid sequence or derivative thereof that interacts with a protein involved in cell wall synthesis or synthesis of other envelope components essential for the 15 integrity of the cell.

31. The polypeptide antibiotic of claim 30, wherein the interaction with the protein inhibits cell wall synthesis or synthesis of other envelope components essential for the integrity of the cell.

32. A method of polypeptide antibiotic killing comprising:

20 contacting a bacterium with a single-gene lysis polypeptide antibiotic, wherein the antibiotic inhibits a target protein involved in cell wall synthesis or synthesis of other envelope components essential for the integrity of the cell, leading to cell lysis upon cell division or continued cell growth.

25 33. The method of claim 32, wherein the target protein is MurA.

34. The method of claim 32, wherein the target protein is MraY.
35. The method of claim 32, wherein the polypeptide antibiotic is a bacteriophage ϕ X174 *E* gene product.
36. The method of claim 32, wherein the polypeptide antibiotic is a bacteriophage Q β *A*₂ gene product.
37. The method of claim 35, wherein the antibiotic is selected from the group consisting of the bacteriophage ϕ X174 *E* gene product, a fragment of the *E* gene product, a derivative of the *E* gene product, or a protein that is homologous or analogous to the *E* gene product.
38. The method of claim 36, wherein the antibiotic is selected from the group consisting of the bacteriophage Q β *A*₂ gene product, a fragment of the *A*₂ gene product, a derivative of the *A*₂ gene product, or a protein that is homologous or analogous to the *A*₂ gene product.
39. A polypeptide antibiotic comprising at least a portion of the *E* gene product which portion interacts with bacterial MraY.
40. A polypeptide antibiotic comprising at least a portion of the *A*₂ gene product which portion interacts with bacterial MurA.
41. The polypeptide antibiotic of claim 39, wherein the antibiotic is the *E* gene product.
42. The polypeptide antibiotic of claim 40, wherein the antibiotic is the *A*₂ gene product.
43. The polypeptide antibiotic of claim 39, wherein the portion of the *E* gene product which interacts with bacterial MraY is selected from the group consisting of: at least a portion of the bacteriophage ϕ X174 *E* gene product, at least a portion of a fragment of the *E* gene product, at least a portion of a derivative of the *E* gene product, or at least a portion of a

polypeptide that is homologous or analogous to a portion of the *E* gene product that interacts with bacterial MraY.

1. The polypeptide antibiotic of claim 40, wherein the portion of the *A₂* gene product which interacts with bacterial MurA is selected from the group consisting of: at least a portion of the bacteriophage Q β *A₂* gene product, at least a portion of a fragment of the *A₂* gene product, at least a portion of a derivative of the *A₂* gene product, or at least a portion of a polypeptide that is homologous or analogous to a portion of the *A₂* gene product that interacts with bacterial MurA.
5
- 10 45. A polypeptide antibiotic comprising at least a sequence that interacts with MraY.
46. A polypeptide antibiotic comprising at least a sequence that interacts with MurA.
47. The polypeptide antibiotic of claim 45, wherein the interaction with MraY inhibits the MraY activity.
15
48. The polypeptide antibiotic of claim 46, wherein the interaction with MurA inhibits the MurA activity.
49. The polypeptide of claim 45, wherein the sequence that interacts with MraY is selected from the group consisting of the bacteriophage ϕ X174 *E* gene product, a fragment of the *E* gene product, a derivative of the *E* gene product, or a protein that is homologous or analogous to the *E* gene product.
20
50. The polypeptide of claim 46, wherein the sequence that interacts with MurA is selected from the group consisting of the bacteriophage Q β *A₂* gene product, a fragment of the *A₂* gene product, a derivative of the *A₂* gene product, or a protein that is homologous or analogous to the *A₂* gene product.
25